3. (Reiterated) A method for promoting survival of dopaminergic cells comprising contacting the cells with a trophic amount of a lipophilic modified *hedgehog* polypeptide.

4. (Reiterated) A method for promoting survival of GABAergic cells comprising contacting the cells with a trophic amount of a lipophilic modified *hedgehog* polypeptide or a lipophilic modified *hedgehog* polypeptide.

11. (Reiterated) The method of any of claims 1-8, wherein the *hedgehog* polypeptide is modified with one or more fatty acid moieties.

REMARKS

Claims 1-21 constitute the pending claims in the present application. Applicants note that claims 5-10, and 12-21 have been withdrawn from consideration, and claims 1-4, and 11 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants respectfully request reconsideration in view of the following remarks.

1. Applicants note with appreciation the Examiner's comments regarding the arrangement of the specifications. Care will be taken to draft future specifications in light of these recommendations.

2. Claims 1-4, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite. As outlined in MPEP 2171, compliance with this paragraph "is evaluated in the context of whether the claim is definite – i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art." Applicants respectfully submit that these claims are directed to subject matter described in the specification in sufficient detail that one of skill in the art would understand the metes and bounds of the subject matter claimed. The specification details many potential uses for lipophilic modified

hedgehog polypeptides including, but not limited to, therapeutic uses in treating human neurological diseases (for example, see Background of the Invention, page 1; Summary of the Invention, page 2; Detailed Description of the Invention, pages 15 and 18-21). The efficacy of such treatments can be monitored in any of a number of ways including, but not limited to, observation of the condition of a human patient monitored by physical examination and clinical tests (for example, see Description of the Invention, pages 10 and 23). One of skill would readily have comprehended these possibilities and others, and Applicants submit that specific monitoring techniques are not required to practice the invention as claimed. Moreover, the results indicated in the preamble of the claims can be achieved without performing a monitoring step. Accordingly, Applicants submit that no particular step of monitoring needs to be recited in the pending claims.

One of skill in the art will also understand that claims 1-4, and 11 read not only on *in vitro* applications of lipophilic modified *hedgehog* polypeptides, but also on *in vivo* uses of the invention, as illustrated by claim 1 which recites a method for promoting survival and/or functional performance of neuronal cells susceptible to excitotoxicity by contacting the cells with an amount of a lipophilic modified *hedgehog* polypeptide effective to reduce excitotoxin-mediated degradation of the cells. Accordingly, Applicants submit that the scope of these claims is not unclear or indefinite. Applicants further point out that *in vivo* and *in vitro* applications of lipophilic modified *hedgehog* polypeptides are linked by claims 1-4 and 11. The Examiner is reminded that, in accordance with MPEP 809, "...linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn."

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

3. Claims 1-4, and 11 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ingham et al., in view of Pepinsky et al. Applicants respectfully traverse this rejection.

Ingham et al. US Patent Number 5,789,543 addresses the use of *hedgehog* polypeptides for regulating differentiation of many cell types. The specification (e.g., Summary of the Invention, paragraph 2) states that "the biological activity can comprise an ability to regulate neurogenesis, such as a motor neuron inducing activity, a neuronal differentiation inducing activity, or a neuronal survival promoting activity." The Office Action correctly points out that Ingham et al., does not disclose the use of lipophilic modifications of *hedgehog* to promote survival and/or performance of neuronal cells.

Pepinsky et al. describe the activity of a lipid-modified *hedgehog* polypeptide. The Examiner asserts that Ingham et al., in view of Pepinsky et al., renders the claims under consideration obvious. Applicants submit that Pepinsky et al. fail to overcome the deficiencies of Ingham et al. Firstly, the lipophilic modified *hedgehog* polypeptides disclosed in Pepinsky et al. were analyzed in one specific murine cell line, C3H10T1/2. This cell line is not a neuronal cell line, but a mesenchymal stem cell line. Applicants submit that one of ordinary skill in the art would not reasonably expect results obtained in this cell line to extend to all cell lines absent further testing not described by Pepinsky et al. A reagent that displays a given set of properties in one type of cell does not necessarily display the same, or even similar, properties in another type of cell, and thus the work described by Pepinsky et al. does not render the invention presently claimed obvious over Ingham et al.

Secondly, the activity of the lipophilic modified polypeptide described in Pepinsky et al. was assessed using an alkaline phosphatase assay. This assay is based on the ability of *hedgehog* polypeptides to induce chondrocyte development in this particular cell line. Alkaline phosphatase serves as an indicator of chondrocyte development, and thus indirectly as an indicator of *hedgehog* activity. Such an assay is not necessarily an indicator of neuronal development or neuronal survival. Thus, the cited art, even in combination, does not provide a reasonable expectation that lipophilic modified *hedgehog* polypeptides would influence neuronal development or survival.

Finally, the work described in Pepinsky et al. assesses the activity of lipophilic modified *hedgehog* polypeptides only in an *in vitro* cell culture system. Pepinsky et al. do not disclose the *in vivo* functionality of such polypeptides. One of ordinary skill in the art would not expect, *a*

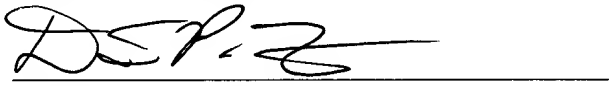
priori, that a lipid-modified *hedgehog* polypeptide would cross the blood-brain barrier, a requirement for an effective therapeutic agent for the central nervous system as set forth in the pending claims. Thus, Pepinsky et al. do not provide a reasonable expectation of success as applied to *in vivo* methods encompassed by the pending claims.

For the reasons stated above, Applicants submit that the proposed combination fails to establish a *prima facie* case of obviousness. The above references fail to teach or suggest the successful use of a lipophilic modified *hedgehog* polypeptide to promote the development and survival of neuronal cells, either *in vitro* or *in vivo*. Absent reasonable expectation of success, the proposed combination renders the claimed invention obvious to try, which is insufficient grounds for a rejection on this basis. MPEP 2143.02. Reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,



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